Recommendations Regarding the Safety and Effectiveness of Hydrocortisone

Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products

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The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (the Topical Analgesics Panel) met from 1972 to 1978 to evaluate the safety and effectiveness of active ingredients in OTC external analgesic drug products. One of the active ingredients reviewed was hydrocortisone (hydrocortisone acetate). Attached is the Topical Analgesics Panel's review of hydrocortisone (published in volume 44 of the Federal Register, December 1979). The panel recommended that hydrocortisone be generally recognized as safe and effective as an OTC antipruritic active ingredient.

to 15 milliamperes was again applied for 5 to 30 minutes. (Ref. 14).

Histamine dihydrochloride has been effectively used as a topical counterirritant in concentrations of 0.025 to 0.10 percent.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.025 to 0.10 percent concentration of histamine dihydrochloride to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical counterirritant active ingredients. (See part III. paragraph B. 1 above—Category I Labeling.

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n. *Hydrocortisone preparations (hydrocortisone, hydrocortisone acetate).* The Panel concludes that hydrocortisone and hydrocortisone acetate are safe and effective for use as OTC antipruritics as specified in the dosage section below. The ingredients depress cutaneous sensory receptors and should bear the labeling for topical antipruritics set forth below.

Hydrocortisone is a naturally occurring steroid found in the adrenal cortex. It is cortisone in which the ketone group on carbon 11 has been converted to a hydroxyl group by the addition of two hydrogen atoms. It is also known as cortisol.

Hydrocortisone is a white powder that is very slightly soluble in water, chloroform, or ether, but is soluble in alcohol. Hydrocortisone is also available as the acetate, which is likewise insoluble in water, and as the phosphate, sodium phosphate, and sodium succinate, which are freely soluble in water.

Hydrocortisone has been marketed in the United States since 1952 as a prescription drug. An effort to change this status was attempted 4 years after its introduction. From August 15 to 17, 1956, FDA held open hearings in Washington, D.C. to examine a petition request for possible transfer of hydrocortisone and hydrocortisone acetate from prescription to OTC status for preparations intended for topical use.

Major discussion centered around three questions: (1) Are ointments and lotions containing not more than 2.5 percent hydrocortisone or hydrocortisone acetate safe for use without a prescription when they are applied to the skin not more than twice daily for not more than 5 days, for the relief of itching and inflammation associated with minor skin irritations? (2) Are ointments or lotions of hydrocortisone or hydrocortisone acetate safe for use without prescription under other conditions of composition and/or labeling? Is a warning against use of such preparations in the presence of infection necessary for safe use without a prescription when the hydrocortisone or hydrocortisone acetate is combined with antibiotic drugs such as oxytetracycline hydrochloride or neomycin sulfate?

Based on this hearing, the Commissioner of Food and Drugs, in a statement published in the Federal Register of January 17, 1957 (22 FR 353), denied the proposed exemption of hydrocortisone and hydrocortisone acetate from current prescription status. The resulting action was based on a failure to show safety for self-medication and a need for more testing for percutaneous absorption.

In the Federal Register of April 28, 1971 (36 FR 7982), FDA listed the pre-1962 topical corticosteroid products recognized as safe and effective. The listing was a result of a review by the National Research Council of the National Academy of Sciences, which had been submitted a short time before. This document stated that 0.5, 1.0, and 2.0 percent hydrocortisone products in different types of vehicles are generally recognized as safe and effective. It was thus established that FDA recognizes that topical hydrocortisone in concentrations of 0.5 to 2.0 percent is safe and effective for steroid-responsive dermatoses when the drug is used as directed as a prescription drug.

(1) *Safety.* Clinical use as a prescription drug has confirmed that hydrocortisone and hydrocortisone acetate are safe in the dosage range recommended by the Panel for use as OTC external analgesics.

(i) *Animal safety data.* The acute oral LD_{50} of hydrocortisone was found to be 1,800±520 mg/kg in male mice, 800±150 mg/kg in female mice, more than 6 g/kg in rats, approximately 175 mg/kg in guinea pigs, and approximately 400 mg/kg in cats (Ref. 1).

A determination was made by Tonelli as to the acute toxicity of corticosteroids, including hydrocortisone in rats, resulting from single subcutaneous injections of each test material in a vehicle containing 0.5 percent carboxymethyl cellulose, 0.4 percent polysorbate 80, and 0.9 percent sodium chloride (Ref. 2). Five groups of eight rats each were injected with 360, 720, 1,080, 1,440, or 1,800 mg/kg of the hydrocortisone preparation. Deaths did not occur until the seventh day following administration. The median lethal dose was determined to be greater than 1,800 mg/kg at day 7,591 mg/kg at day 14, and 449 mg/kg at day 21. Throughout the study there were no deaths among the rats treated with the vehicle alone. Autopsies of several corticosteroid-treated animals revealed multiple small abscesses in the lungs, kidneys, and/or liver.

To test his hypothesis that the principal causes of death among the test animals were due to supervening infections and generalized septicemia, Tonelli repeated the above study and added 0.1 percent chlortetracycline, a broad-spectrum antibiotic, to the diet of one-half of the test animals. The number of deaths among the hydrocortisone-treated rats receiving the medicated diet was significantly reduced. During the 21-day study, only 4 of 40 hydrocortisone-treated rats receiving the medicated diet died, compared with 29 of 40 hydrocortisone-treated animals receiving the nonmedicated diet. The median lethal dose for the hydrocortisone-treated animals receiving a medicated diet was greater

than 2,400 mg/kg at days 7 and 14 and approximately 2,400 mg/kg at day 21. Tonelli concluded that "Corticosteroid lethality increased with time. The principal cause of death was a generalized septicemia, as evidenced by abscess formation in major organs presumably due to suppression of the animal's immune-response mechanism. Concomitant administration of a broad-spectrum antibiotic reduced the toxicity of four of the five corticosteroids tested." The Panel notes that Tonelli also concluded that hydrocortisone was found, based upon median lethal dose determinations, to be significantly less toxic than any of the six other glucocorticoids [i.e., triamcinolone, triamcinolone acetonide, dexamethasone, prednisolone, 21-deoxytriamcinolone acetonide, and 9 *alpha*, 11 *beta*-dichloro-21-hydroxy-16 *alpha*, 17 *alpha*-(isopropylidenedioxy)-1, 4-pregnadiene-3,20-dione) tested in both of the above studies.

Subacute toxicity studies performed by various investigators viewed the effects of corticosteroids on total body weight loss, and the long-term effects of inhibition or reduction of deoxyribonucleic acid (DNA) synthesis on various body structures including circulating lymphocytes.

Such studies performed by Stevens et al. in adrenalectomized mice supported previous findings that corticosteroids with certain molecular structures "diminish the mass of lymphatic tissue and decrease the number of circulating lymphocytes" apparently "by bringing about destruction and enhancing the maturation and death of lymphocytes as well as inhibiting their proliferation" (Ref. 3). The test animals received intraperitoneal injections of 1 mg hydrocortisone acetate in 0.25 mL 0.9 percent saline, and then received injections of 1 microcurie thymidine-2-^{14}C at various times before being sacrificed 30 minutes after the later injection. The time intervals studied ranged from 7 to 360 minutes after the administration of the hydrocortisone acetate preparation. There was a significant decrease in the weight of the spleen per 100 g of body weight after 120 and 360 minutes and in the weight of the thymus per 100 g of body weight after 360 minutes. Neither the spleen, thymus, nor lymph nodes showed a significant change in the total amount of DNA or ribonucleic acid (RNA) apparently "due to the phagocytosis of nuclear and cytoplasmic debris by macrophages and preferential loss of other cytoplasmic constituents." The lymph nodes and thymi showed a significant decrease in the incorporation of thymidine-2-^{14}C into DNA at 120 minutes and thereafter. Stevens et al. concluded that "whatever other effects corticosteroids have on lymphocytes, they do inhibit the synthesis of DNA as measured by the incorporation of thymidine-2-^{14}C." According to Stevens et al., two factors may be responsible for the inhibition of DNA synthesis in the thymi and lymph nodes produced by hydrocortisone: a destructive effect of the hormone on the lymphocytes and the effect of the hormone on metabolic processes in such cells, the result of which is a decrease in DNA synthesis.

Ingle et al. demonstrated the quantitative differences in the biologic properties of corticosterone and its oxygenated derivative, hydrocortisone (Ref. 4). Subcutaneous injections of various amounts (0.5 to 5.0 mg daily) of each compound in a sesame oil vehicle (0.5 mL per injection) were administered in divided daily doses to 5 infection-free male rats immediately following force feedings of a high carbohydrate diet. At the 5-mg daily dose, glycosuria with hyperglycemia was induced in 80 percent of the test animals receiving hydrocortisone (maximum glycosuria value of more than 9 g of gulcose daily) as opposed to 40 percent of those receiving corticosterone (maximum glycosuria value of over 2 g daily). At this daily dosage level, hydrocortisone produced a more marked loss of body weight and a greater increase in the excretion of sodium, chloride, potassium, and nitrogen. At lower daily doses, hydrocortisone, but not corticosterone, produced a temporary increase in sodium, chloride, and nitrogen excretion and caused a definite loss of body weight.

As a followup to published reports that glucocorticoids inhibit mitosis and have been demonstrated autoradiographically to inhibit the healing of gastric ulcer and regeneration of the liver after partial hepatectomy, Lahtiharju et al. (Ref. 5) conducted an autoradiographic study comparing the effect of a single corticosteroid dose on DNA synthesis of cells of the stomach and other organs in white male mice. The abdominal cavities of the test animals were injected with single doses of 1.0 mg hydrocortisone or 0.05, 0.1, or 0.5 mg dexamethasone followed by an injection of 1 microcurie per gram (μC/g) of ^{3}H-thymidine 5 hours later. Control animals initially received injections of physiological saline. The animals were decapitated 1 hour after receiving the ^{3}H-thymidine injection. Autoradiograms of tissue samples were prepared, and the percent ratio (thymidine index) of the labeled cells was counted. After a single does of either of the two corticosteroids, "a significant decrease in DNA synthesis was established autoradiographically in the epithelial cells of the mouse stomach and a slight decrease was established in the duodenal cells and the cells of the liver mesenchyma." The investigators observed that the corticosteroid-treated mice showed no evidence of hepatocyte inhibition.

Ingle and Meeks studied the biologic effects of continuous subcutaneous injections of hydrocortisone and cortisone in normal male rats force-fed a medium carbohydrate diet (Ref. 6). Aqueous solutions of 1, 2, or 4 mg of each corticosteroid in 5 percent ethanol and 0.9 percent sodium chloride were administered by continuous subcutaneous injection for 10 days. The third load remained constant at 20 mL/rat/day. The investigators reported that "the indices of hypercorticalism were weight loss, negative nitrogen balance, glycosuria, atrophy of the adrenal cortex and of the thymus, and gross pathologic changes, such as renal damage and stomach ulcers. The extent of response was related to the dose of each steroid. The quantitative activity of hydrocortisone was approximately twice that of cortisone as indicated by each of the several indices of hypercorticalism."

Investigation into the safety of hydrocortisone use on healing tissues has also been reviewed by the Panel. Reynolds and Buxton observed aberrations produced by exogenously administered hydrocortisone in healing regenerative tissue of male albino rats (Ref. 7). The test animals were wounded by excising a 2-cm circle of skin, extending to, but not including, underlying fascia, from the shaved dorsum of each animal. On the fifth postwounding day, 15 test animals received intramuscular injections of 25 mg/kg hydrocortisone daily for 6 days. The investigators reported that "administration of exogenous hydrocortisone inhibits contraction of open skin wounds, with lysis of cell components and increasing both protein and non-protein nitrogen components, but particularly the non-protein fraction." The large amounts of non-protein nitrogen fragments suggested, and microscopic examination confirmed, a reduction in fibril formation, and high glutamic oxalacetic transaminase (GOT) concentrations indicated a sustained cell destruction which was also confirmed by microscopic examination. A simultaneous accumulation of sialic acids indicated a continuing polysaccharide matrix. A hypocellular

and hypofibrillar wound with delayed contraction and little tensile strength thus resulted.

Vogel studied the effects of corticosteroids on wound tensile strength in male rats when the corticosteroids were administered at various phases in the wound-healing process (Ref. 8). An incision approximately 3 cm long was made down to the fascia in the shaved dorso-lumbar region of each test animal. The test animals received daily subcutaneous injections of 5 or 50 mg/kg hydrocortisone and were sacrificed on days 3, 6, 9, 12, or 20 following wounding. Wound tensile strength was decreased between days 3 and 9 in direct proportion to the dose administered, with the greatest decrease occurring on day 6. Vogel reported the following:

On the 12th day and even more distinctly on the 20th day after operation, a reversal of this effect could be observed. Low doses of glucocorticoids resulted in an increase in wound tensile strength, whereas high doses, already toxic after prolonged administration, still caused a decrease. If treatment was started at the end of the collagen phase (11th day), only an increase in wound tensile strength was seen, regardless of the dose of glucocorticoid administered. Short-term treatment during the scar phase (day 19 to 20) resulted in an increase in wound tensile strength which correlated with the dose and potency of the glucocorticoid given. It is therefore concluded that scar tissue of wounded skin reacts like normal connective tissue as far as the increase in tensile strength induced by glucocorticoids is concerned.

Corticosteroids can alter the functions of various enzymes and hormones in the body, as shown by various studies of these effects and their relation to the organ system. Pomerantz and Chuang found that subcutaneous injections of hydrocortisone in hamsters resulted in a decrease in tyrosinase activity which could be prevented by concurrent administration of B-melanocyte stimulating hormone (MSH) (Ref. 9). The investigators reported that hydrocortisone may lower tyrosinase by blocking the release of endogenous MSH and that "it seems likely that conditions in man and other mammals that result in elevated levels of MSH are associated with increases in skin tyrosinase and that the increased enzyme produces the dark skin or hair pigmentation."

Hall and Hall administered 0.5 mg of the water-soluble phosphate form of hydrocortisone twice daily by subcutaneous injection to nine female Holtzman strain rats for 21 days. Then one test animal was sacrificed. No appreciable thymic or adrenal atrophy was evident in this test animal at necroscopy, and none of the remaining animals showed significant growth retardation. One mg of a microcrystalline acetate suspension of hydrocortisone was administered once daily by subcutaneous injection to the eight remaining test animals. All animals were sacrificed on day 51 of the study. The investigators reported that inhibition of growth rate was slight during the first 11 days when the phosphate ester of hydrocortisone was administered but became pronounced when the acetate form was substituted (Ref. 10). Macroscopic examination at the time of autopsy showed marked adrenal and thymic atrophy and hypertrophy of the preputial glands. Histologic examination revealed no evidence of cardiac pathology, although the glomeruli of the kidneys "showed intense and irregular capillary dilatation with hypertrophy of the visceral lamina of Bowman's capsule, and the presence of the same curious vesicular structures as have been found to result from cortisone overdosage."

A number of the published studies reviewed by the Panel discuss effects of various doses of corticosteroids on both thymolytic activity and permeability changes in the vascular systems of the body. The systemic anti-inflammatory activities as measured by thymolytic activity of hydrocortisone, betamethasone, and six commercially available topical steroid preparations (i.e, 0.1 percent betamethasone valerate lotion, 0.025 percent fluocinolone acetonide lotion, 0.1 percent triamcinolone acetonide lotion, 0.05 percent flurandrenolone cream, 0.1 percent fluperolone acetate ointment, and 0.02 percent flumethasone pivalate lotion) were compared by Child et al. in intact male and female weanling WAG strain albino rats and female ICI mice. The results were comparable to their topical vasoconstrictor activity in healthy human subjects (Ref. 11). The steroids were injected subcutaneously into the test animals twice daily for 2 successive days, and the thymus glands were removed and weighed on day 3. The relative potency of each steroid was calculated using as metameters the logarithm of the dose and the thymus weight (mice) or the square root of the thymus weight (rats) with covariance corrected for initial body weight. Using the vasoconstrictor test described by McKenzie and Atkinson (Ref. 12), Child et al. applied serial dilutions of each steroid to the flexor surfaces of both forearms of male and female human subjects. After 16 hours the occulsive dressings were removed and the forearms were examined for vasoconstricted patches. Hydrocortisone was found to be the least active, both topically and systemically, among all the steroids tested. Except for betamethasone and betamethasone valerate, there was close correlation betwen the topical and systemic activity rankings of each steroid within the group. The topical activity of hydrocortisone was calculated to be less than 0.1 based on a value of 100 established for fluocinolone acetonide. Hydrocortisone ranked sixth in the group in terms of topical activity. It is important to note that Child et al. concluded, "Although comparison of activity in animals and man is limited by species variation and route of administration, the agreement shown between the ranking orders of topical and systemic activities suggest that in general they are related."

Weston et al. investigated the cellular effect of hydrocortisone on tuberculin reactions in guinea pigs relative to determining the mechanism by which hydrocortisone suppressed delayed hypersensitivity reactions (Ref. 13). One week after sensitization with complete Freund's adjuvant, tuberculin-sensitized Hartley strain guinea pigs received intraperitoneal injections of 10 mg (0.4 mL) hydrocortisone daily for 4 days. Control animals received daily injections of 0.4 mL intraperitoneal saline for 4 days. The investigators reported that "differential cell counts of biopsy specimens revealed that cortisol treatment resulted in a greater reduction in macrophages than small lymphocytes. This disproportionate reduction in macrophages, viewed from the migration inhibitory factor (MIF) model of delayed hypersensitivity, shows that either the sensitized lymphocyte is unable to produce and release MIF or the macrophage itself cannot respond to MIF when treated with cortisol." It was further reported that hydrocortisone therapy consistently resulted in an actual decrease in the diameter of both erythema and induration, and that it significantly reduced the intercellular edema of the epidermis associated with tuberculin skin tests. Retesting three months following hydrocortisone therapy showed the skin tests of the treated and untreated animals were quite similar, thus indicating that the suppressive effect of hydrocortisone was not permanent under the conditions of this study. Weston et al. concluded that the study suggests that hydrocortisone "is exerting its effect on the recruitment or migration of non-

sensitized cells, rather than by eliminating the sensitized lymphocyte itself."

Lykke, Willoughby, and Houck (Ref. 14) studied the effects of hydrocortisone-released protease preparations from rat skin upon the vascular permeability of the rat as a followup to the findings of Houck and Patel (Ref. 15) and Spector (Ref. 16). Houck and Patel observed that, after the injection of hydrocortisone, the extracellular and extrafibrillar compartment of rat skin contains a nonlysosomal, neutral pH optimal proteolytic enzyme that can be inhibited by both soybean trypsin inhibitor and salicylates (Refs. 15 and 17). Spector determined that some proteolytic enzymes are capable of increasing the permeability of the microcirculation (Ref. 16) Hydrocortisone-released protease preparations were prepared from the shaved and cleaned skin of 3 groups of 12 male Sprague-Dawley rats 26 hours after the subcutaneous injection, and 2 hours after the intraperitoneal injection, of 3 mg/kg hydrocortisone. For control purposes, similar preparations were prepared from rats that received injections of the carrier solvent for the above hydrocortisone preparation. Lykke, Willoughby, and Houck (Ref. 14) determined that extracts from the hydrocortisone-treated rats contained a protease, whereas this protease was lacking in extracts from the skin of untreated rats. These investigators reported that intradermal injections of low concentrations of the hydrocortisone-released protease preparation into the shaved abdominal skin of rats resulted in increased vascular permeability and emigration of leukocytes. They concluded, however, that "this protease appears to exert its vascular permeability-enhancing effect by a mechinism that would not seem to rely on the release or activation of many of the well recognized mediators" (i.e., release of histamine and serotonin or formation of vasoactive kinins). According to Lykke et al., a potent permeability factor associated with the systemic treatment of rats with steroids "could well explain the apparent lack of effect of steroids on acute inflammation consisting mainly of increased vascular permeability * * * whereas it is effective against the more chronic type of inflammatory lesion."

Paulsen and Rerup demonstrated that hydrocortisone was capable of penetrating the skin of rats and exerting systemic effects as indicated by involution of the thymus (Ref. 18). One-tenth mL of the acetate or free alcohol form of various concentrations (0.25, 0.5, or 1.0 percent) of hydrocortisone solutions or suspensions in several vehicles (i.e., polyethylene glycol, olive oil, chloroform plus olive oil, physiological saline, or ointment base) was evenly applied once daily for 3 days to the shaved backs of 24- to 28-day-old female rats. Immediately after each application, the treated area was protected by a collar placed around the neck, and the animals were then isolated in glass jars for 2.5 hours. After that time, the shaved areas were washed with acetone to remove possible residues of the hydrocortisone compound. The test animals were sacrificed 72 hours after the first application, and the thymus of each rat was then removed and weighed. The control animals were shaved, handled, and isolated in the same manner as the hydrocortisone-treated animals. The investigators reported that "both the absolute thymus weights and the thymus weights per 10 g of body weight were reduced to less than 30% of those of the control group after cutaneous application of hydrocortisone" and that the difference was highly significant (p = less than 0.001). Paulsen and Rerup could detect no significant difference in results between the various media in which hydrocortisone was dissolved or suspended. A significant dose-response relationship was established once the values were corrected for body weight variance.

In a study conducted by Tonelli, Thibault, and Ringler, the thymolytic activity in rats of various concentrations (250 to 16,000 μg/mL) of hydrocortisone in a 1-percent croton oil vehicle was determined. Each test material was applied topically to the right ear of each of six rats. For control purposes, the vehicle was applied to the right ears of 10 rats. Six hours later both ears of each animal were removed and weighed. Forty-eight hours after application of the above hydrocortisone preparations and vehicle, the test animals were sacrificed, and the thymi were then removed, weighed, and expressed as mg thymus/100 g of body weight. The investigators reported that the effects of the 500 and 1,000 μg/mL concentrations of hydrocortisone on thymus weight were not significant but were highly significant at higher concentrations. They further determined on the basis of radioactivity data that between 22.7 and 28.8 percent of the amount of hydrocortisone applied to the animals' ears was absorbed during the first 6 hours following application (Ref. 19).

The Panel recognizes that demonstration of safety is an essential factor for consideration in topical application of cortisones to the skin. The following animal studies were reviewed by the Panel to observe effects due to systemic absorption or alterations to the skin surface when directly treated.

Baker and Montes noted histochemical changes in the skin of rats following topical applications of a 1-percent hydrocortisone in 25 percent ethanol solution for a period from 61 to 140 days (Ref. 20). Twice daily throughout the study, 0.1 mL of the hydrocortisone solution was applied to an area just caudal to the right ears of 39 Long-Evans rats. The hair in this area was clipped initially and at weekly intervals thereafter. For control purposes, 0.1 mL of the 25-percent ethanol solvent was similarly applied to identical test sites on 39 Long-Evans rats of the same average body weight (314 g). Skin samples were excised from both the treated area on the right side of each animal's neck and from the left, or untreated, side at the termination of the study, with the result that each animal served as its own control. The investigators reported that "treatment with alcohol alone did not modify the skin significantly." They noted, however, that after prolonged local application of hydrocortisone, "Nonspecific esterase was reduced in sebaceous glands. Total DPN diaphorase and lactic dehydrogenase activities were reduced in epidermis coincident with thinning of this structure. These enzymes, in addition to succinic dehydrogenase and cytochrome C oxidase, remained active in the smaller cells of the treated epidermis. Nonspecific esterase, DPN diaphorase, lactic dehydrogenase, and cytochrome C oxidase were depleted from connective tissue cells and the external epithelial sheath of the hair follicle as they underwent involution due to hormone action."

Castor and Baker observed cutaneous modifications resulting from prolonged topical application of various adrenocortical hormones, including hydrocortisone on nontraumatized skin (Ref. 21). Various adrenocortical hormones in a 25-percent alcohol solution were applied daily to the skin of the neck, caudal to the right ear, of 43 adult rats for as long as 180 days. Cortisone and hydrocortisone were administered in daily doses of 25 to 100 mg dissolved in 0.1 mL 25 percent alcohol. Several animals received 0.1 mL daily of a 25-percent alcohol solution of an extract derived from hog adrenal glands which, in terms of liver glycogen units, was equivalent to 1 mg/mL cortisone. For control purposes, 23 test animals received daily applications of

0.1 mL of the 25-percent alcohol solvent. At various times during the study, microscopic examinations were made of biopsies of skin taken from symmetrical areas behind the ears. The investigators summarized their findings as follows:

> The prolonged percutaneous application of adrenocortical hormones modified the histology of the skin, the changes induced being limited to the area of treatment. The epidermis became thinner and, in males, the size of the epidermal cells was reduced. Growth of hair ceased and sebaceous glands became smaller. The thickness of the dermis was reduced, apparently due to loss of substance from the collagenous fibers, the elastic fibers remaining numerous in spite of the treatment. Fibroblasts and other cells of the dermal connective tissue were fewer in number.
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> The development of a state of refractoriness to the action of the hormones was demonstrated by the resumption in growth of hair in the area of application when treatment was continued for 180 days.

(ii) *Human safety data.* On review of the literature, the Panel found no report on aggravation of cutaneous bacterial, fungal, or virus infection attributable to the topical application of hydrocortisone-containing products (Ref. 22).

A submission reviewed by the Panel made reference to the reports of more than 90 clinical studies, involving more than 12,000 human subjects, that have been published during the first 21 years following the introduction of topical hydrocortisone preparations in 1952 (Ref. 23). Only 222 adverse reactions were reported in these studies. These were all of a minor nature and were primarily attributed to the vehicle or to a contaminant rather than to hydrocortisone. In these studies, hydrocortisone was substantiated as being the causative agent in only 2 of 95 subjects who were treated with topical hydrocortisone preparations and who experienced sensitization or irritation reactions characterized by erythema, desquamation, and itching. In most instances the effects were minor among the 95 subjects who complained of mild itching and burning at the site of application. These effects were attributed to the irritating properties of the vehicle and did not result in discontinuance of treatment. The available literature contains infrequent reports of cases of allergic contact dermatitis from topical hydrocortisone preparations, but in most of these cases patch testing did not demonstrate that hydrocortisone was the sensitizing agent (Ref. 23).

This submission included copies of 19 publications reporting striae formation, atrophy, telangiectasia, and other dermal manifestations which followed topical applications of flourinated steroids and topical applications or systemic use of corticosteroids other than hydrocortisone (Ref. 23). Adam and Craig in 1965 indicated that "no cases of striae formation have been reported with the older steroids, such as hydrocortisone, which suggests that the newer steroids have a more potent effect on dermal connective tissue elements" (Ref. 24).

Hydrocortisone and other steroids are used to treat a variety of dermatologic conditions, especially those accompanied by inflammation. The following set of studies deals with safety considerations concerning histological changes in tissue structure or the possibility of super-infection.

Sneddon noted aggravation and extension of telangiectasia in 14 patients suffering from rosacea and treated by prolonged topical application of flourinated steroids. Termination of treatment in most cases was followed by severe rebound inflammatory changes characterized by edema and acute pustular eruption. Sneddon reported that hydrocortisone, used together with oral tetracycline, did not produce the same effects (Ref. 25). Stevanovic, however, reported corticosteroid-indiced atrophy of the skin with telangiectasia in six patients. One patients was a female who applied a hydrocortisone preparation to the upper eyelids as a cosmetic for several years (Ref. 26). According to Stevanovic, histological examination "suggested that the first changes in the dermal tissue occur in the ground substance, followed by those of elastic and collagen fibers. These changes are ascribed mainly to the incomplete inhibition of fibroblasts by the corticosteroid." Stevanovic indicated that the atrophy with telangiectasia induced by hydrocortisone "can best be explained by its very prolonged used and the special microanatomical features of infected skin."

Goldman, O'Hara, and Baskett reported that 45 biopsies performed on normal skin areas following local intradermal injections of a hydrocortisone acetate suspension produced "hematoxylinophilic masses persistent over a considerable period of time" and that "Preliminary histochemical studies suggest that these are ground substance changes" (Ref. 27). These investigators further reported that 42 biopsies performed on skin with a variety of inflammatory conditions, and following local injection of a hydrocortisone acetate suspension, "revealed definite inhibition of inflammation in the eczematous, toxic (not too severe), tuberculin, psoriatic, sarcoidal, neurodermatitic keloidal, lymphomatous and leukemic skin reactions and also in some miscellaneous disorders." In contrast, "Biopsies of the urticarial reaction and the local histamine wheal have revealed no significant changes." Goldman later reported that "detailed studies, after local application of both ointments and lotions of the hydrocortisone acetate and free alcohol . . . have shown no histopathologic reactions in normal skin" and that "chromatographic and colorimetric assay controls with hydrocortisone acetate and free alcohol also have revealed no evidence of absorption, in spite of definite local clinical responses" (Ref. 28).

In studies conducted by Fleischmajer, two patients treated with prolonged topical applications of a 2.5-percent hydrocortisone ointment for pathologic skin conditions "developed pustular eruptions and crusting, apparently as a result of secondary infection in skin areas affected by severe excoriations from scratching" (Ref. 29). The infection disappeared, however, following local and systemic administration of antibiotics, without any interruption of the topical hydrocortisone treatment. In another study, 708 patients, most of whom suffered from various types of eczema confined to small skin areas, were treated with topical applications of hydrocortisone, in various formulations, as the acetate or free alcohol, and in concentrations ranging from 0.25 to 2.5 percent. The eczematous lesions worsened in 22 cases (approximately 3 percent) following such treatment (Ref. 30). The investigators reported that "sometimes changing to another ointment base was helpful." Patch testing never showed hypersensitivity to hydrocortisone, but occasional intolerance to all available hydrocortisone products has been shown. Its complete failure, in certain cases where a response might be expected, is unexplained. In a few cases, increased infection has occcured, e.g., *Staphylococcus aureus* in seborrhoeic eczema. On the other hand, it was reported that there seems to be little or no evidence that hydrocortisone ointment positively favors superficial infections. More recent double-blind studies conducted by Carpenter et al. (Ref. 31) revealed that topical applications of a 1.0 percent hydrocortisone cream, three times daily, to patients with acute dermatoses (primary diagnosis of contact, eczematoid, or atopic dermatitis, neurodermatitis, or intertriginous eruption, complicated by suspected

secondary bacterial or fungal infections, produced no increase in infection 7 to 10 days after the initiation of treatment. There was a significantly greater overall response of the lesion and symptomatic improvement, compared with patients treated similarily with the base or cream alone. Pathogens were distributed evenly among the two treatment groups, and *Staphylococcus aureus* was the most frequent contaminant. Seven to 10 days following the initiation of treatment, 31 percent (21 of 68 patients) of the hydrocortisone-treated group were pathogen-negative, compared with 27 percent (18 of 68 patients) of the base cream-treated group.

Wachs, Clark, and Hallett (Ref. 32) treated 100 patients suffering from psoriasis, atopic dermatitis, or various eczemas and dermatoses, with topical applications of either betamethasone valerate or fluocinolone acetonide two or three times daily for 3 weeks. Both of these corticosteroids are more potent than hydrocortisone and were applied in a random, double-blind manner without the use of occlusive dressings. The above investigators reported "no change either in the patient's bacterial flora or in the incidence of fungal isolation" and concluded that "it may be that the threat of overgrowth after routine topical treatment does not exist, or has been overemphasized."

A submission reviewed by the Panel referred to eight clinical studies, published between 1954 and 1957, in which some patients experienced irritation or aggravation of their condition after topical applications of hydrocortisone preparations. In almost all instances, the irritation or aggravation subsided with continuing treatment or a change in the hydrocortisone vehicle base (Ref. 23).

The Panel thoroughly reviewed literature concerning the safety of hydrocortisone. Strong emphasis was placed on isolating cases of adverse reactions. According to a submission reviewed by the Panel, only three cases of serious adverse effects from the use of topical hydrocortisone preparations have been documented in the literature between 1952, when such preparations were first introduced, and late 1973, when the submission was prepared (Ref. 23).

In 1962 Fanconi reported a case of an infant with generalized eczema who experienced a temporary retardation of growth while receiving total body inunction with a 1.0-percent hydrocortisone ointment, twice daily for 6 months (Ref. 33).

Benson and Pharoah in 1960 reported a case of a 5½-year-old boy who had suffered from chronic eczema since the age of 6 months and who had been treated with a nongreasy 1-percent hydrocortisone alcohol ointment for 18 months before being hospitalized. He had developed vomiting and coughing that continued for 1 week before hospitalization. The child also experienced bilateral frontal headaches 3 days before treatment was sought (Ref. 34). Upon examination, the subject showed evidence of growth retardation (i.e., 42-inch height was less than third percentile), bilateral papilledema of moderate severity due to benign intracranial hypertension, and accelerated weight gain during topical hydrocortisone treatment. Hydrocortisone treatment was discontinued at the time of hospitalization, and the symptoms disappeared in a few days. The papilledema also disappeared rapidly and the fundi regained their normal appearance within 4 weeks.

Feinblatt et al. in 1966 reported a case of a 3-week-old male infant who received topical applications of 0.25 percent hydrocortisone with tetracycline phosphate complex and amphotericin B in an "acid-mantle lotion," three times daily for a period of 8½ days, for the treatment of epidermolysis bullosa lesions. During that period the infant received a total of 300 mg hydrocortisone or 2,100 mg/m^2 of body surface area. By the fourth day of treatment, a rapid gain in body weight was noted; puffy eyelids and pitting edema of the legs were also observed. At that point the use of the lotion was discontinued. Two days later the rapid increase in body weight ceased, but the infant remained edematous for about 1 week (Ref. 35).

In the three cases cited above, the topical applications of hydrocortisone preparations were excessive. The applications were made either for prolonged periods of time or were made over extensive areas of the body. In each case, however, the clinical status of the subject returned to normal following the discontinuance of topical hydrocortisone treatment. The latter two patients cited in the cases above showed abnormal vital signs. The 3-week-old infant experienced rapid breathing, and the 5½-year-old boy had a pulse rate of 90/ minute and a blood pressure of 95/95. Their vital signs, however, returned to normal after topical hydrocortisone treatment was discontinued.

In more than 12,000 subjects treated with topical hydrocortisone and 90 clinical studies and almost 30 experimental or safety studies, no other abnormal vital signs were reported (Ref. 23). These same studies also revealed abnormal laboratory findings for bloo chemistry, liver function tests, or routi urinalysis.

During the last 20 years a variety of absorption, excretion, and metabolism studies have been conducted to evalu the extent of percutaneous absorption topically applied hydrocortisone preparations and the systemic effects percutaneous absorption. These studie have established that percutaneous absorption does indeed occur, but that is always at such a low level that it is unlikely to cause systemic effects similar to those that occur following systemic administration of the drug (i. Collagen degeneration, cutaneous stri formation, osteoporosis, overt diabete or high blood glucose, hypokalemia, electrocardiographic abnormalities, muscular weakness, detectable psychological abnormalities, peptic ulcer, and supression of the adrenal axis).

In 1956 Scott and Kalz conducted autoradiographic studies of skin biopsies after topical application of a 1 percent radioactive hydrocortisone ointment to the normal skin of the upp back of six subjects. Results suggested that some systemic absorption occurre Autoradiographs of normal skin 1 hour after application of the ointment demonstrated that the readioactive hydrocortisone had been "distributed through the epidermis, with slightly more dense accumulation near the surface. After 2 hours, there was a high concentration of the material in the basal layer of cells. Dispersion of C^{14} was seen to have occurred through the dermis after 6 hours, with apparent collection of the material around the blood vessels; the basal layer still contained a quantity of the isotope however. After 16 hours, little or no radioactive particles remained in the section of skin, suggesting the systemic absorption of the C^{14}" (Ref. 36). These investigators observed that there appeared to be no difference in the course of absorption, whether the preparation remained on the skin 2 hours or 6 hours. They concluded that "once epidermal penetration had occurred, the process of subsequent absorption proceeded without interruption." Their investigation reportedly dispels the hypothesis that the main route of topical hydrocortison absorption is via the hair follicles and the orifices of glands. They noted that there was no more rapid appearance of C^{14} in the skin adjacent to such structures than in the remainder of the skin immediately subjacent to the epidermis on other sites.

Later studies reported by Malkinson in 1958 (Ref. 37) revealed that no significant absorption of hydrocortisone by normal skin occurred 5½ to 6 hours after topical application of a radioactive hydrocortisone ointment to eight sites on the flexor surface of the forearm of four human subjects. Malkinson further reported that there was no evidence of hydrocortisone absorption following application of a radioactive hydrocortisone ointment to normal skin and before and after exposure of the skin sites to an erythema-producing dose of ultraviolet light. When this ointment was applied to a total of five skin sites in three subjects immediately following stripping, gas-flow cell measurements detected evidence of C^{14} absorption at all test sites. There were levels of residual radioactivity ranging from 52 to 84 percent within the first 5 minutes after application. Radioactivity at these sites had decreased to anywhere from 16 to 37 percent of original levels after 1 hour, and to 10 to 22 percent after 4 to 6 hours. Malkinson remarked, however, that it was not surprising to him that penetration of hydrocortisone-4-C^{14} in normal skin was not detected by the gas-flow cell, because the quantitative absorption of this compound "is well within the inherent percentage of error of this device." He had found previously, from detection of radioactivity in urine extracts, that hydrocortisone-4-C^{14} is "absorbed from normal skin in small quantities approximately 1 to 2 percent of the topically applied material" (Ref. 38).

Studies conducted by Greaves demonstrated that there is some in vivo destruction of hydrocortisone (Ref. 39). Hydrocortisone that contained tritium was applied under occlusion to the skin of the abdomen, forehand, and/or scrotum of a normal male and female subject. After 12 hours, less than 0.5 percent of the radioactive hydrocortisone applied to the abdomen was detectable in the urine and occurred predominantly as 17-oxysteroids. Seventeen percent of the radioactive hydrocortisone that was applied to the scrotum was excreted as corticosteroids, with a distribution of metabolites similar to that following oral administration of hydrocortisone. Greaves feels the data suggest that hydrocortisone "When topically applied loses its side chain before reaching its site of action in the cells and so becomes physiologically inactive. The greater potency of triamcinolone and fluocinolone acetonides administered percutaneously may be in part due to the fact that their side chains cannot be cleaved."

Feldmann and Maibach performed studies in which they quantitated the effect of regional variation in normal male subjects on the percutaneous penetration of hydrocortisone (Ref. 40). They reported that absorption is increased in regions with large or numerous hair follicles and is decreased in some regions having thickened stratum corneum. These generalizations, however, do not apply to absorption through the palm of the hand and scrotum. There was significant absorption from the palm of the hand, even though it has a fairly thick stratum corneum and no hair follicles. The scrotum presented almost no barrier to hydrocortisone penetration. Feldmann and Maibach indicated that "other determining factors may be present in these regions of obvious specialization in structure and function." The Maximum C^{14} urinary excretion rate was achieved during the second 12-hour period for all areas except the foot, where the maximum rate was reached on the third and fourth days, and the back, where the maximum rate was reached on the second day. The above investigators reported the following maximum C^{14} urinary excretion rates per 24 hours, in percent of the applied dose of hydrocortisone: 0.32 percent for the ventral part of the forearm, 0.62 percent for the dorsal part of the forearm, 0.04 percent for the plantar foot arch, 0.14 percent for the lateral ankle, 0.29 percent for the palm of the hand, 0.40 percent for the back, 1.74 percent for the scalp; 1.28 percent for the axilla, 5.09 percent for the forehead, 7.84 percent for the jaw angle, and 27.7 percent for the scrotum.

Another study by Feldmann and Maibach (Ref. 41) revealed that "between 0.2 and 1.0 percent of hydrocortisone, applied to normal skin appears in the urine over a period of ten days. Stripping the skin doubles this amount and significantly alters the absorption rate curve. An occlusive dressing increases absorption ten-fold but does not basically alter the absorption rate curve. Evidence is presented suggesting that both the stratum corneum and the Malpighian/basal layers serve as skin barriers."

Percutaneous absorption studies by Feinblatt et al. in normal male children less than 2 years old revealed that an average of 21.6 percent of a hydrocortisone-4-C^{14} cream, applied topically under occlusion to the antecubital fossae, was recovered in the urine within 5 days (Ref. 35). An average of 35.6 percent was recovered under similar conditions from the urine of subjects with atopic eczema, whose ages ranged from 2 months to 18½ years. The recovery rates were highest during the first 2 days after application and declined progressively on subsequent days. The investigators concluded that when hydrocortisone is topically applied under occlusion "a significantly large amount of percutaneous absorption of hydrocortisone occurs through the skin of children. The tendency to use topical steroids indiscriminately must be condemned. When it is required, the amount of drug placed on the skin should be given consideration."

When administered orally or parenterally, hydrocortisone preparations tend to cause a lowering in circulation of eosinophiles. The following studies were performed to determine the extent to which this occurs when the drug is used topically. Thorn et al. in 1948 reported that the intramuscular administration of a single dose of 25 mg purified pituitary adrenocorticotropic hormone to normal subjects and patients with diseases not involving the adrenal cortex consistently produced a marked decrease (approximately 50 percent) in circulating eosinophils within the first 4 hours (Ref. 42).

A study reported by Smith in 1953 (Ref. 43) indicated that "there was no consistent alteration in the circulating eosinophile count after the inunction" of 6 g of a 25-mg/g hydrocortisone acetate ointment on the back, upper arms, and legs of each of eight normal adult subjects. Circulating eosinophile counts were performed the day prior to inunction and at 4, 6, and 28 hours after inunction. Similar results were obtained when the same ointment was applied to the affected areas of seven patients with generalized skin disease. Smith concluded that the data indicate "that there was either no absorption or, at any rate, insufficient absorption to produce a drop in the circulating eosinophile count. It is of course possible that the test used as a criterion of absorption and systemic effect was not sufficiently sensitive to demonstrate blood changes which might result from the absorption of very minute amounts of hydrocortisone. It is however unlikely that the small amounts which would thus escape detection could account for the therapeutic effects reported."

Gemzell, Hard, and Nilzen conducted a study reported in 1954 in which 48 subjects, some of whom were normal and some of whom had very mild mycosis of the feet, a slight dermatitis of the hands, or minor psoriasis plaques,

received a topical application of 200 mg hydrocortisone incorporated into various vehicles. The application was rubbed on the anterior surface of the body from the neck to the knees for 10 minutes (Ref. 44). In all cases the topical application of hydrocortisone was followed by an increase in the plasma levels of 17-hydroxycorticosteroids within 1 hour, but the investigators did not consider this rise to be statistically significant. Two hours after inunction, a decrease ranging from 6 to 34 percent in the circulating eosinophil count was noted. The investigators did not consider this decrease significant because among the control group there was a decrease of approximately 25 percent in the circulating eosinophil count 2 hours after inunction. They indicated, however, that "even if the figures are not statistically significant, they nevertheless suggest a general effect. It is possible that more sensitive methods than those used in this investigation would be necessary to show such an effect. A more sensitive method is not available at present."

The results from an investigation conducted by Fleischmajer and reported in 1961 "strongly suggest that external hydrocortisone treatment does not produce any major systemic effects following the use of large amounts over prolonged periods of time" (Ref. 29). Ten females and 9 males, ranging in age from 5 to 60 years, received topical applications of a 2.5-percent hydrocortisone ointment twice daily over a 3- to 20-month period. The total amount of hydrocortisone applied per subject ranged from 8,750 to 95,000 mg. Fifteen subjects were being treated for atopic dermatitis, one for atopic dermatitis in combination with ichthyosis, and three for lichen simplex chronicus. Three months after initial treatment, the circulating eosinophil count had decreased in 4 subjects, but the count remained unchanged or had increased slightly in the remaining 15 subjects. Other laboratory tests, including a white blood cell differential count, a urinary 17-ketosteroid determination, and quantitative assays of blood glucose and serum electrolytes, were periodically performed. None of these showed any distinct changes.

In the above study conducted by Gemzell, Hard, and Nilzen, five subjects received a subcutaneous injection of 0.5 mg/kg hydrocortisone. It was reported that "the plasma levels of steroids rose in one hour from 13.0 to 19.4 μg per 100 mL of plasma, then fell. The number of eosinophils decreased continuously throughout the 6-hour period and reached the low level of about 50 percent of the initial value." One subject was given 1 mg/kg hydrocortisone in oral tablet form. The investigators reported that for this subject "the plasma level of 17-hydroxycorticosteroids rose in two hours from 17.3 to 69.5 μg, and the eosinophils decreased to zero in the six-hour period" (Ref. 44). These results, according to the investigators, agreed well with previously reported findings on the use of oral hydrocortisone.

Feinblatt et al. in 1966 commented, however, that "depression of eosinophil counts has been accepted in the past as specific evidence of the circulating level of hydrocortisone-like hormones in the blood. In addition to the fact that the amount of hydrocortisone needed to depress eosinophils has not been documented, many investigators have reported on the variability and lability of eosinophil counts and the inadequacy of this method as a means of determining 17-hydroxycorticosteroid levels" (Ref. 35).

The above study by Gemzell et al. (Ref. 44) demonstrated that subcutaneous injection or oral administration of hydrocortisone increases the plasma levels of 17-hydroxycorticosteroids, attaining the maximum levels in 1 to 2 hours. Neither this study nor Fleischmajer's study discussed above (Ref. 29) demonstrated any distinct or significant change in the plasma level of 17-hydroxycorticosteroids or urinary level of 17-ketosteroids following topical application of hydrocortisone.

On the basis that a "suppression of the urinary 17-ketosteroids and an increase in the 17-hydroxycorticosteroids is the expected finding following the systemic administration of hydrocortisone," Smith attempted to show that systemic absorption of topically applied hydrocortisone does occur, by demonstrating an alteration in urinary steroids. He applied 10 g of a 25-mg/g free-alcohol form of hydrocortisone ointment to the back, arms, and thighs of eight normal male adult subjects (Ref. 45). However, Smith found that there was no consistent alteration in the urinary 17-ketosteroids or 17-hydroxycorticosteroids after inunction with the test material, nor was there any significant difference in the above urinary steroid levels following inunction with the ointment base alone. He concluded that "these results indicate that either there was no absorption or there was insufficient absorption to alter these urinary steroids."

A study conducted by Witten, Shapiro, and Silber, reported in 1955, revealed that the "inunction of relative large body areas of normal or diseased skin with 30 g of ointment containing 7 mg hydrocortisone acetate over a 3-da period does not increase the 17,21-dihydroxy-20-ketosteroid levels in urin and blood" (Ref. 46). The study involve six normal adult males, and three females and six males with extensive c generalized skin disease (bullous erythema multiforme, allergic eczematous contact-type dermatitis, pemphigus foliaceus, and psoriasis). Determinations were made immediatel following the collection of urine and blood specimens taken 12 hours after the last topical application of the abov hydrocortisone ointment. It was concluded by these investigators that "the findings lend further support to th mass of clinical evidence indicating tha there are no dangers to be anticipated from absorption and consequent systemic effects of therapeutic quantities of hydrocortisone applied topically in ointment form even to large areas of altered skin for long periods o time."

Scoggins and Kliman (Ref. 47) reported the case of a 22-year-old male with psoriasis of 6 years' duration whic had become severe and generalized during the 11 months preceding the study period. Initially, 400 mg hydrocortisone in a cream base was applied daily for 3 days to approximately 20 percent of the body surface. After an intervening control period of at least 9 days, two applications of hydrocortisone with an occlusive dressing, which totalled 1,200 mg hydrocortisone daily, were made to 90 percent of the body surface. The investigators reported that "the smaller dose of hydrocortisone caused a decrease in eosinophil count on the 1st day of treatment and a moderate rise in plasma cortisol concentration. The absorption of small amounts of this dru was difficult to document because the methods used do not permit differentiation between exogenous and endogenous cortisol. The large dose of hydrocortisone produced unmistakable evidence of the presence of exogenous cortisol—that is, a threefold increase in plasma cortisol concentration, marked increases in the steroid content of the urine—and a prompt decrease in eosinophil count." They further reporte that "when the large amount of hydrocortisone was applied, sodium excretion was almost completely suppressed, and there was a transient rise in potassium excretion." It was indicated that the amount of 17-hydroxycorticosteroids that is excreted in the urine after daily topical

administration of 1,200 mg hydrocortisone suggests that less than 10 percent of the dose was absorbed. They concluded that without an occlusive dressing, systemically significant amounts of the corticosteroids are absorbed only if the dose applied is very large.

McCorriston (Ref. 48) reported no elevation above normal levels of 17-ketosteroids, creatinine, or corticoids in a 15-year-old female during the 4-week period that the subject applied a 2.5-percent hydrocortisone acetate ointment to her face, neck, both antecubital fossae, and both wrists.

The final concern for safety, highlighted in the remaining studies, deals with prolonged use of steroid products. Questions on steroid accumulation resulting in excess levels in the body, and problems caused by steroid withdrawal are answered based on information appearing in literature over the years.

In "The Pharmacological Basis of Therapeutics," Sayers and Travis reported that administration of large doses of hydrocortisone for prolonged periods "produces changes in carbohydrate and protein metabolism that are, in general, the converse of those in adrenocortical insufficiency. Blood sugar tends to be high, liver glycogen is increased, and there is increased resistance to insulin. The catabolic action of the steroid is reflected in the wasting of tissues, reduced mass of muscle, osteoporosis (reduction in protein matrix of bone followed by calcium loss), and thinning of the skin. In certain instances, a diabetic-like state may be produced" (Ref. 49).

The report in the above study by Scoggins and Kliman involving the 22-year-old male with psoriasis indicated that there was no discernible change in glucose tolerance following the topical application of 1,200 mg hydrocortisone, under an occlusive dressing, to 90 percent of the body surface during a 1-day period. Nor was there a discernible change in glucose tolerance following the daily topical application of 400 mg hydrocortisone, without an occlusive dressing, to 20 percent of the body surface during a 3-day period (Ref. 47).

In the study by Fleischmajer, no definite changes in blood glucose levels could be found in any of the 19 subjects who received topical applications of a 2.5-percent hydrocortisone ointment twice daily over a 3- to 20-month period (Ref. 29).

Munro and Clift (Ref. 50) demonstrated "that patients with chronic skin disease using the quantity of corticosteroid ointments commonly prescribed in general practice and hospital outpatient clinics, are not significantly at risk from adrenal axis suppression." Insulin stress tests were used to determine whether adrenal axis suppression was present in 40 outpatients suffering from eczema or psoriasis and treated with topical corticosteroids for prolonged periods. Thirty-one patients (77.5 percent) had received treament for 3 to 6 years. The subjects applied one or more of the following corticosteroids topically, under occlusion by polyethylene film (50 percent of patients), polyethylene gloves, or coverings over relatively small areas of their skin: 0.1 percent betamethasone 17-valerate ointment (22 patients used this alone), 0.025 percent fluocinolone acetonide, 0.025 percent beclomethasone dipropionate, and small amounts of 1.0 percent hydrocortisone acetate ointment.

The investigators report as follows: "Of the forty patients studied thirty-seven (92.5%) had a normal response on first testing . . . . When the tests were repeated in the three cases with initial abnormal results after 2–5 months with the patients using half their previous dose of topical corticosteroid ointment, all the patients had essentially normal results (one was minimally below the normal range with a maximal level of 19.5 μg/100 mL and an increment of 12 μg/100 mL)." The three patients with abnormal results initially were using 25, 30, and 100 g betamethasone ointment weekly. The first two used polyethylene film occlusion over large areas of their bodies for a 10- and 2-year period, respectively, when their skin disorder was troublesome. The third patient was a small female for whom a weekly dose of 100 g over a 3-year period represented an especially large dose.

Corticosteroids occur naturally in the body. An excess production of corticosteroids or adrenal insufficiency can easily upset homeostatic balance and cause systemic manifestations and alarming symptoms. Possible absorption through the skin of a topically applied hydrocortisone product is an important issue when considering the safety of hydrocortisone in OTC topical antipruritic preparations. The complications of excessive corticosteroids in the body include electrolyte imbalance, hyperglycemia, glucosuria, susceptibility to superinfection due to inhibition of macrophages, and the classical picture of Cushing's syndrome. These characteristics are warnings of systemic buildup.

Numerous tests have been performed on the absorption of topically applied hydrocortisone preparations. Many are reviewed in the preceding section on human safety. Fleischmajer (Ref. 29) applied a 2.5-percent hydrocortisone acetate ointment twice daily to the skin of 19 patients with atopic dermatitis. The study extended over a 3- to 20-month period. The total dose of hydrocortisone applied ranged from 8,750 to 95,000 mg. No characteristic side effects were noted. Seven patients showed some increase in body weight, but there were no changes in eosinophil counts, in white cell differential count, in urinary 17-ketosteroid analysis, or in blood glucose and serum electrolytes values.

Feldmann and Maibach (Ref. 41) noted that following the topical application of C^{14}-hydrocortisone, only 0.2 to 1.0 percent appeared in the urine. The effect of occlusive dressing on the absorption of topically applied corticoids was studied by Feinblatt (Ref. 35). Ten mongoloid subjects with normal skin were treated with C^{14}-hydrocortisone and the treated areas were occluded with polyethylene film. Urinary recovery of hydrocortisone from these subjects averaged 21.6 percent, a 20-fold increase over subjects with nonoccluded areas. However, this difference is not major, and there are no systemic problems associated with it.

The quantity of topically applied hydrocortisone that is absorbed depends upon such factors as the dose of hydrocortisone and the size and location of the area treated (Ref. 40). As stated above, the following percentages represent the amount of C^{14}-hydrocortisone absorbed from various areas of the body: 0.32 percent from the ventral forearm, 0.62 percent from the dorsal forearm, 0.04 percent from plantar foot arch, 0.14 percent from the lateral ankle, 0.29 percent from the palm, 0.40 percent from the back, 1.74 percent from the scalp, 1.28 percent from the axilla, 7.84 percent from the angle of the jaw, and 27.7 percent from the scrotum (Ref. 40). If the ointment is applied to small areas, none of these percentages will reflect a significant increase in systemic corticoid activity. Treatment of a large area, such as the total body area, requires that attention be given to the period of use of the hydrocortisone ointment. Rare systemic effects can occur after prolonged application and when large areas of the body are treated. Only 3 actual cases have been reported during a 21-year period of use of topical hydrocortisone. The changes which occurred were temporary, and the symptoms disappeared when treatment was discontinued (Ref. 23).

Local changes may occur in the skin after long-term application of hydrocortisone, but the incidence is rare and usually results from secondary infection. A change in the type of ointment base used has often caused the

symptoms to regress or disappear [Refs. 29 and 30].

Allergic reactions to cortisone and its derivatives have been reported, but they are rare (Ref. 23). On review of the literature, the Panel found no reports on the aggravation of cutaneous bacterial, fungal, or viral infections attributable to the topical application of hydrocortisone-containing products. Based on the numerous safety studies available and on the long history of topical use, the Panel concludes that hydrocortisone and hydrocortisone acetate are generally recognized as safe for OTC topical use as antipruritics in doses up to 0.5 percent concentration.

(2) *Effectiveness.* There are studies documenting the effectiveness of hydrocortisone and hydrocortisone acetate in the dosage range recommended by the Panel for use as OTC external analgesics.

Hydrocortisone and hydrocortisone acetate are classified as external analgesics because of their effectiveness on the skin as antipruritic agents. Hydrocortisone preparations have had wide usage in the topical treatment of dermatoses and are preferred for topical use over cortisone because they are active on the skin (Ref. 51).

Hydrocortisone and hydrocortisone acetate are two of the most potent and effective agents for the treatment of many common dermatoses. Numerous controlled and uncontrolled studies provide strong documentation for their efficacy as antipruritic and anti-inflammatory agents in the 0.5 to 5 percent dosage range (Ref. 52). In recent years newer studies have investigated the topical use of concentrations in the dosage range of 0.1 to 0.25 percent.

The following table summarizes the studies that are relevant to the topical use of hydrocortisone preparations:

Controlled Studies Demonstrating Effectiveness of Topical Hydrocortisone

Investigator	Disease state	Dosage (percent)	Evaluation
Becker (Ref. 53)	Pruritus ani/vulvae	1.0	89% of patients showed improvement.
Bisley (Ref. 54)	Pruritus ani/vulvae, eczema	1.0	80% of patients had symptomatic relief.
Botta (Ref. 55)	Eczema, psoriasis lichen planus, various dermatoses.	1.0	90% showed relief.
Carpenter et al. (Ref. 31)	Common dermatoses with secondary bacterial or fungal infections.	1.0	Average of 73.5% of patients improved in all states.
Carter et al. (Ref. 56)	Seborrheic eczema	1.0	74% of patients fast relief.
Clyman (Ref. 57)	Various dermatoses	1.0	Improvement not too significant.
Clyman (Ref. 58)	Eczema, lichen simplex chronicus, dermatosis.	0.5	Showed effective in 70% of cases.
Eskind (Ref. 59)	Contact dermatitis	0.2 to 2.5	Some improvement, especially at the high dosage.
Fisher (Ref. 60)	Lichen planus	1.0	40% effective, but no improvement with control at all.
Frank (Ref. 61)	Various pruritic dermatoses	0.25	Effective antipruritic.
Frank et al. (Ref. 62)	Various dermatoses	0.5 to 1.0	Both dosages showed effectiveness.
Goltz (Ref. 63)	Various dermatoses	1.0	61% showed fast complete improvement.
Haeger (Ref. 64)	Hypostatic eczema (stasis dermatitis).	1.0	73% improved as compared to placebo control ointment.
Heileson et al. (Ref. 65)	Various dermatoses	1.0	51% more activity than inactive control.
Heileson et al. (Ref. 66)	Eczema	1.0	59% of patients who used it improved.
Hill (Ref. 67)	Eczema	1.0	In 74% of patients strong improvement.
Howell (Ref. 68)	Various dermatoses	1.0	88% of patients improved.
Miller (Ref. 69)	Various dermatoses	1.0	76% of patients improved.
Peristein (Ref. 70)	Nummular eczema	1.0	98% of patients relieved of pruritus and lesions.
Phillips (Ref. 71)	Various dermatoses	1.0	79.2% of patients had symptomatic improvement.
Polano (Ref. 72)	Pruritus/eczema	1.0	90% of patients showed improvement.
Portnoy (Ref. 73)	Dermatitis/eczema	1.0 to 2.5	64% of patients improved with lower dosage.
Rattner (Ref. 74)	Various dermatoses	0.5 to 1.0	1% better; both dosages effective.
Robinson et al. (Ref. 75)	Various dermatoses	0.5 to 2.5	Less than 1% concentration relatively ineffective.
Robinson et al. (Ref. 76)	Various dermatoses	0.5 to 1.0	34% of patients improved with the low dosage; 67% of patients improved with the 1% concentration.
Robinson et al. (Ref. 76)	Various dermatoses	0.5 to 2.5	Higher percentage (82 to 92%) improvement with oily base than with greaseless base.
Russell et al. (Ref. 77)	Eczema, dermatitis, lichen simplex.	1.0	Only 38% completely relieved.
St. John's Staff (Ref. 30)	Eczema, dermatitis	1.0	65% showed relief of itching, reduction of inflammation, or complete suppression of physical signs.
Stevens et al. (Ref. 3)	Effectiveness measured by lymphocyte response.	0.5 to 1.0	Both dosage levels are active.
Turell (Ref. 78)	Pruritus ani/vulvae	1.0	32% totally cleared.
Wartzki et al. (Ref. 79)	Pruritus, eczema	1.0	64% showed good improvement.
Way (Ref. 80)	Acne	0.25	85% relieved of irritation, erythema.
Welch et al. (Ref. 81)	Various dermatoses	0.5 to 2.5	0.5% may be less effective in severe acute state otherwise equal effectiveness as the 1.0 and 2.5% ointments.
Wilson et al. (Ref. 82)	Eczema, pruritus	1.0	79% showed good to moderate improvement.
Witten et al. (Ref. 83)	Various pruritis	0.1 to 0.5	0.1% dosage helpful; the higher concentration worked well.
Zelcer (Ref. 84)	Various pruritic dermatoses	0.25	Good effect.
Zelcer (Ref. 85)	Various pruritic dermatoses	0.125	Worked in most cases.

Dosage is an important factor in the determination of therapeutic effectiveness. Hydrocortisone preparations have been marketed in a dosage range of 0.5 to 2.5 percent concentrations. It is the Panel's opinion that OTC products should contain the lowest effective dosages. Data that evaluate the effectiveness at low dosage levels are reviewed below.

Frank implemented a study to compare the effectiveness of hydrocoritsone as an antipruritic agent at concentrations of 0.1 and 0.25 percent. The hydrocortisone was incorporated into two different bases to evaluate the effects of the base media on the various pruritic dermatoses. The use of the 0.25 percent preparations resulted in an improvement in the condition in all cases, and relief from itching was almost immediate. At the 0.1-percent level, results from the test preparations could not be differentiated from those of the control preparations (Ref. 61).

A study by Isaac Zelcer further supports the effectiveness of 0.25 percent concentration of hydrocortisone preparations. In this study, 159 patients were treated with 0.25 percent hydrocortisone acetate ointment. The nature of the skin diseases varied and included eczema, contact dermatitis, atopic eczema, seborrheic eczema, dyshidrosis, lichenification, and pruritus ani and vulvae. In most cases, the treatment successfully relieved symptoms of the various skin diseases. It is important to note that a wider range of skin conditions was reviewed in this study, and that the hydrocortisone acetate ointment was, at times, used as other than an antipruritic agent. Failures occurring in this study were attributed to early discontinuance of treatment (Ref. 84).

Hydrocortisone preparations are frequently used as anti-inflammatory agents. They are prefered to cortisone for two reasons. First, local application of hydrocortisone preparations have a more constant anti-inflammatory effect. Second, hydrocortisone preparatons can be used in lower concentrations than cortisone and still be effective. It is interesting to note that despite hydrocortisone's potency, there are no reports of irritation or senstitivity due to it. Where senstitivity has occurred, it was determined that the ingredients in the base vehicle were the causative agents (Ref. 85).

A study conducted by Welch compared the effectiveness of a wide range of topical hydrocortisone concentrations. As other studies have indicated, hydrocortisone preparations are effective for many dermatoses. This study does point out one important factor. The concentrations studies were

equally effective in most cases, but in the acute phase of most dermatoses or in chronic dermatoses associated with lichenification, doses below 0.5 percent were not always effective (Ref. 81).

Hydrocortisone preparations have been used successfully in the topical treatment of many skin diseases. Hydrocortisone prepartions are safe and effective for mild contact dermatitis, transient atopic dermatitis, mild infantile eczema, uncomplicated status dermatitis, and idiopathic pruritus vulva or ani.

In a study by Witten on the treatment of infantile eczema, hydrocortisone was effective in relieving the condition (Ref.46). Interestingly enough, wide body areas were treated, and there were no problems of super-infection.

Over the past 21 years, numerous studies have reported on the effectiveness of topical hydrocortisone preparations as antipruritic and anti-inflammatory agents. The Panel believes that adequate information has been presented and reviewed to support the conclusion that hydrocortisone and hydrocortisone acetate may be used safely and effectively as OTC external analgesics in short-term therapy within the dosage range specified below.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.25 to 0.5 percent concentration of hydrocortisone or hydrocortisone acetate to affected area 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below-Category I Labeling.) In addition, the Panel recommends the following specific labeling for products containing hydrocortisone and hydrocortisone acetate as external (antipruritic) analgesic active ingreients: *Indication.* "For the temporary relief of minor skin irritations, itching, and rashes due to ecxema, dematitis, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, and jewelry, and for itchy genital and anal areas."

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o. *Juniper tar.* The Panel concludes that juniper tar is safe and effective for use as an OTC external analgesic as